

The role of inflammation and anti-inflammatory medication in asthma

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Abstract Asthma is a chronic inflammatory disease of the airways involving a wide range of cells and mediators. First-line therapy of persistent asthma involves the use of inhaled corticosteroids to control the underlying inflammation of the airways. Inhaled β_2 -agonists are also widely used in asthma therapy and are the most effective bronchodilators currently available. The short-acting β_2 -agonists are now used on an as-needed basis for rapid relief of symptoms. In recent years, long-acting inhaled β_2 -agonists have had an increasing role in the management of asthma, particularly in patients with moderate to severe asthma. This class of drug has a long duration of action and is recommended as add-on treatment to inhaled corticosteroids in the long-term control of asthma. New therapies have been added to asthma therapy as our understanding of the pathogenesis of asthma has increased. The use of multiple therapies necessitates a clear understanding of the mode of action of the drugs and any potential interaction or overlap of effect. For many people asthma is associated with complex therapy; thus treatment developments that simplify asthma treatment are an important step forward in asthma management.

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INTRODUCTION

Asthma is a complex condition that results from the interactions of a variety of environmental factors acting on a background of genetic predisposition. It is characterized by airway inflammation, reversible airway obstruction and airway hyper-responsiveness to a variety of stimuli.

Asthma can also be a progressive disease that is treated with a range of therapies according to the severity of the disease. Indeed, different aspects of asthma need to be treated with different agents in order to achieve symptom control. First-line therapy involves the use of inhaled corticosteroids to control the underlying inflammation of the airways. Short-acting β -agonists provide rapid relief of bronchoconstriction in all patients with asthma, whereas long-acting β_2 -agonists, which have a long duration of action, control asthma symptoms and can reduce the frequency of exacerbations when added to inhaled corticosteroids (1,2). The long-acting β_2 -agonist formoterol has a unique clinical profile, combining a fast onset and long duration of action (3).

Asthma treatment guidelines have been developed in several countries, including the USA (4,5) and the UK (6). The aim of the guidelines is to achieve optimal asthma

control with the lowest possible dose of medication. Within the guidelines it is recognized that inflammation of the airways is present even in mild persistent asthma, and the evidence of a role for corticosteroids in suppressing inflammation in asthma is reviewed extensively. Consequently, the control of inflammation has a prominent place in asthma management.

Current guidelines recommend a stepwise approach to the treatment of asthma in both adults and children. Progression to the next step up is indicated when control is not achieved or is lost at the current step, while the patient is adherent to prescribed medication. Stepping up treatment involves stepping up from the use of short-acting β -agonists (as symptom relievers) to inhaled corticosteroids (as controllers of inflammation) and then to the use of inhaled corticosteroids and inhaled long-acting β_2 -agonists (4–6). Using this stepwise approach, both the inflammatory process of asthma and the concomitant bronchoconstriction can be effectively managed (2).

AIRWAY RESPONSE IN ASTHMA

The early asthmatic response (EAR), which is triggered by exposure to inhaled antigens or irritants, causes bronchoconstriction. This acute response is caused when allergens cross-link to immunoglobulin E (IgE) bound to the surface of the mast cells causing the mast cells to release a number of inflammatory mediators, including

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histamine, prostaglandins and cysteinyl-leukotrienes. This mediator release results in smooth muscle contraction and mucosal oedema. The EAR can also be triggered by airborne antigens binding to sensitized mast cells on the mucosal surface of the airways. This type of response, although caused by inflammatory mediators, can be completely inhibited or reversed by bronchodilators such as β_2 -agonists. The anti-inflammatory action of inhaled corticosteroids is mainly due to direct inhibition of transcription factors that are normally activated by inflammation. Thus, they have little effect in the short term against the early response mechanism, which tends to give rise to immunological reactions (2,7).

The late asthmatic response (LAR), which may follow the EAR, involves acute inflammation and swelling of the airway wall. Approximately 4–6 hours after an antigen challenge, activated neutrophils, eosinophils, mast cells and T lymphocytes migrate into the airways causing inflammation. This in turn may lead to epithelial desquamation, changes in mucociliary function, reduced clearance of respiratory tract secretions, and thus airway obstruction (2). The LAR is often followed by an increase in airway hyper-responsiveness that can be measured by bronchial provocation with histamine or methacholine.

AIRWAY INFLAMMATION IN ASTHMA

Histological studies of the bronchial mucosa have been instrumental in establishing the inflammatory basis of asthma. These studies have highlighted the wide range of cells and mediators involved in the pathophysiological process underlying asthma.

Bronchoalveolar lavage (BAL) studies in patients with asthma have clearly demonstrated increased numbers of eosinophils and mast cells in the affected airways. Other

cell types are also known to contribute to the inflammatory events, including T lymphocytes and macrophages (8). All of these cells are known to have a crucial role in chronic airway inflammation through secretion of pre-formed and newly synthesized mediators that act either directly on the airway (9,10) or indirectly through neural mechanisms (4,11). Mucosal inflammation is characterized by increased T lymphocyte activation, mast cell degranulation and accumulation of activated eosinophils in the airways. These markers correlate with both variable airway flow and airway hyper-responsiveness (12). To date, the exact relationship between individual inflammatory cells and their mediators, and hyper-responsiveness of the airways and clinical symptoms, remains unclear (8). There is also evidence which points to a pro-inflammatory role for structural cells in asthma, including epithelial and endothelial cells, fibroblasts and airway smooth muscle (8). The development of hyper-responsiveness is at least in part determined by epithelial injury, and this can be mediated by immunological and non-immunological mechanisms (11).

Thus, all of these cell types are important target cells in the treatment of asthma and current anti-inflammatory corticosteroid therapy is thought to have direct inhibitory actions on many of the inflammatory cells implicated in asthma (see Figure 1).

Eosinophils

The eosinophils are the most characteristic inflammatory cells in bronchial biopsies taken from asthma patients and may be seen in the submucosal and epithelial layers. Activated eosinophils have been associated with tissue destruction (13). Eosinophils present in the airways are recruited from bronchial circulation after specific interaction with adhesion molecules expressed on the

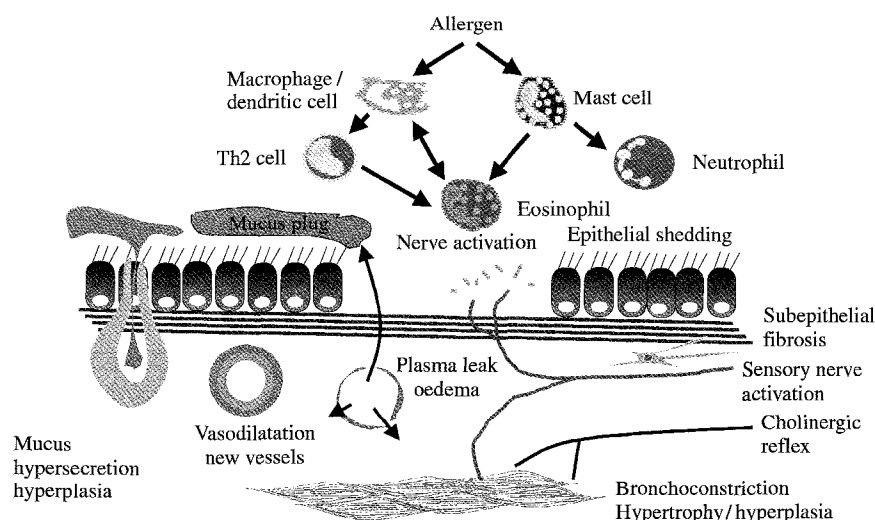


Figure 1. Cellular mechanisms involved in airway inflammation.

endothelium (9). Eosinophil mediator secretion in asthma has been confirmed by BAL, which shows increased concentrations of granule-derived basic proteins (14). It is unlikely that cytokine secretion from the eosinophils or mast cells is the primary source of cytokines involved in the EAR, since it is the macrophages—acting as antigen presenting cells—that release the ‘first wave’ of cytokines. These cytokines then act on the epithelial cells to release a second wave of cytokines (10). Eosinophils have been shown to selectively damage the bronchial epithelium through the release of mediators such as the basic proteins contained in specific eosinophil granules and active oxygen radicals (9).

T lymphocytes

T lymphocytes may also have an important role in initiating early inflammatory events in the airways. Activated T helper (CD4⁺) lymphocytes are present in bronchial biopsy specimens and BAL fluid of asthma patients (11, 13,15). The degree of activation of T lymphocytes in BAL fluid correlates with both the number of eosinophils in BAL fluid, as well as with the severity of symptoms and the degree of bronchial hyper-responsiveness (15). The T helper lymphocytes have been classified into subgroups of cells which release different patterns of cytokines and so mediate the allergic response of asthma. Th2 type cells release a pattern of cytokines that are involved in allergic inflammation, including IL-4, IL-5, IL-9 and IL-13. In atopic individuals, the balance is tipped in favour of Th2 cells.

Mast cells

Increased numbers of mast cells have been identified in the bronchial epithelium using electron microscopy and BAL (9). In normal airways the number of mast cells increases towards the periphery of the lung, a region not accessible to endobronchial biopsy. However, the lungs of patients who have died from asthma show a substantial increase in mast cells, particularly outside the airway smooth muscle (9). The change in distribution of the mast cells within the asthmatic lung and the correlation between the number of mast cells and disease severity strongly support a role for mast cells in the pathophysiology of the disease (9,16). Current evidence also provides a case for mast cell-derived histamine as the major component of adenosine-induced bronchoconstriction (16).

Mast cells may also have a role in persistent or chronic inflammatory responses through the release of multi-functional cytokines. The evidence which supports this hypothesis includes the localization of immunoreactivity for IL-3, IL-4, IL-5, IL-6 and GM-CSF to mast cells in human bronchial biopsies (16). Mast cells, in normal and asthmatic airways, contain tryptase as their major neutral protease. Tryptase is localized within the mast cells

and has been used as a marker of mast cell degranulation. Increased concentrations of this protease have been found in lavage fluid in asthma patients (9).

Macrophages

Macrophages secrete cytokines, including IL-1, interferon- γ , TNF- α , IL-6 and IL-8 (11). As effector cells they have additional pro-inflammatory functions in airway inflammation, being involved in the removal of cellular debris and having the ability to migrate to sites of inflammation (11). Their ability to secrete bioactive lipids, platelet-activating factors, reactive oxygen species, nitric oxide and nitrates has beneficial effects on vascular smooth muscle tone and bronchial epithelial cells, and possibly on bronchial smooth muscle tone (11). However, macrophages may also inhibit allergic inflammation through the secretion of various inhibitory mediators, including prostaglandin E₂ and IL-10. The secretion of these inhibitory mediators may be impaired in patients with asthma (17).

Structural cells

The constituent cells of the airway, including fibroblasts, endothelial cells and epithelial cells, also contribute to the inflammatory process by releasing inflammatory mediators such as cytokines and chemokines (1).

Airway microvascular leakage is another important component of airway inflammation which contributes to airway oedema and causes obstruction, bronchial hyper-responsiveness and the formation of mucus plugs in the peripheral airways. Exuded plasma, via plasma mediators, also adds to airway inflammation and airway narrowing (18).

ASTHMA THERAPY: LINKING MECHANISM OF ACTION TO CLINICAL EFFICACY

Anti-leukotriene drugs

Leukotrienes are inflammatory mediators formed from arachidonic acid via the 5-lipoxygenase pathway. The cysteinyl leukotrienes LTC₄, LTD₄ and LTE₄ are potent bronchoconstrictors that have several biological actions in the pathogenesis of asthma, including increased vascular permeability, formation of oedema and enhanced mucus production. Currently available anti-leukotriene drugs can act by decreasing the production or action of leukotrienes and they are the first agents used in the treatment of asthma to target specific steps in the inflammatory pathway rather than the general suppressive effect of corticosteroids.

Although studies suggest that anti-leukotriene drugs may be beneficial in asthma (19), more recent studies

show that they are much less effective than very low doses of inhaled corticosteroids and are therefore not a substitute as first-line therapy (20). They are also less effective than long-acting inhaled β_2 -agonists as add-on therapy in asthma (21).

Long-acting β_2 -agonists

The β_2 -agonists are very effective bronchodilators, and short-acting inhaled β_2 -agonists provide rapid relief of asthma symptoms. Formoterol and salmeterol are currently the only long-acting inhaled β_2 -agonists available for use in asthma patients, and they provide bronchodilation for at least 12 hours. This longer duration of action makes the long-acting β_2 -agonists suitable for maintenance therapy and the control of nocturnal asthma symptoms (22). Formoterol and salmeterol also have a higher affinity for β_2 -adrenoceptors than salbutamol. Although formoterol and salmeterol belong to the same class of long-acting β -agonists, they are very different pharmacologically. Salmeterol is a partial agonist at β_2 -adrenoceptors whereas formoterol is a full agonist with a higher level of intrinsic efficacy at the β_2 -adrenoceptor, giving a greater airway smooth muscle response, especially when muscle tone is increased (23).

Mechanism of action and onset and duration of action

The β_2 -agonists bind to the β_2 -adrenoceptor, causing activation of the receptor and subsequent stimulation of adenylate cyclase with the formation of cyclic AMP. Cyclic AMP acts as an intracellular mediator to relax the bronchial smooth muscle and thus achieves bronchodilation. Cyclic AMP also inhibits the release of inflammatory mediators from mast cells (22,24).

Formoterol and salmeterol are derived from a substituted catecholamine ring structure with an extended hydrophobic side-chain. Anderson (25) has proposed the plasmalemma diffusion microkinetic hypothesis to explain the mode of action of long-acting β -agonists in the immediate vicinity of the β_2 -adrenoceptor. Formoterol, a moderately lipophilic compound, is partitioned between the aqueous phase and the lipid membrane. In the aqueous phase, formoterol is available to activate the receptor rapidly; however, sufficient formoterol is retained and subsequently released from the membrane to account for its long duration of action. Salmeterol, on the other hand, which is highly lipophilic, has a partition equilibrium in favour of the lipid compartment. In this case, most of the agonist passes into the lipid membrane and there is little available to activate the receptor, thus accounting for the slow onset of action (25). Bronchodilation begins within 3 minutes of inhalation of formoterol 12 μ g, which compares well with the short-acting

β -agonists, and is maximal within 60 minutes. After a similar inhalation of salmeterol 50 μ g, however, response begins after 10 minutes and has a later peak (24).

In addition to relaxing bronchial smooth muscle, the long-acting β_2 -agonists also have some anti-inflammatory properties, although they are not effective on the same inflammatory responses that are so effectively suppressed by corticosteroids (18). Using a guinea-pig model, Tokuyama *et al.* showed that topical formoterol was an effective inhibitor of histamine-induced airway microvasculature leakage and airflow obstruction. Formoterol was 35 times more potent than salbutamol (18). In a recent double-blind, randomized, placebo-controlled study to investigate the effects of a single dose of inhaled formoterol or salbutamol via Turbuhaler® on airway responsiveness to AMP and histamine, we showed that formoterol had a probable mast cell-stabilizing effect in patients with mild asthma, whereas salbutamol did not (26). In a second study in mild atopic asthma patients, formoterol significantly reduced the number of submucosal mast cells compared with pre-treatment, with a similar trend for eosinophils (27).

The long-term use of β_2 -agonists is associated with a desensitization of the β_2 -adrenoceptor (23). Tolerance to the bronchoprotective and bronchodilator effects of β_2 -agonists has been described by several authors (28–30). While tolerance to the bronchoprotective effect appears well established, tolerance to the bronchodilator properties of long-acting β_2 -agonists is more contentious. Some studies report tolerance to the acute bronchodilatory response within 4 weeks of regular treatment and others show sustained improvements in indices of airway obstruction for up to 12 months (31–34).

The down-regulation of pulmonary β_2 -adrenoceptors, with a concomitant decrease in β_2 -adrenoceptor mRNA expression, has been reported after long-term β_2 -agonist monotherapy (2). The full clinical significance of this is unclear, since other researchers have shown that long-term corticosteroids up-regulate β_2 -adrenoceptors (35). Assuming patients with asthma receive anti-inflammatory medication in the form of corticosteroids, potential receptor down-regulation may be prevented.

Corticosteroids

Corticosteroids are the most effective treatment for asthma currently available, and inhaled corticosteroids are now the mainstay of asthma therapy. The recognition of an early role for inflammation in the pathogenesis of asthma has led to the introduction of inhaled corticosteroid treatment at an earlier stage in therapy. In fact, inhaled corticosteroids are now recommended for all patients who have symptoms more than twice weekly (5) or who require an inhaled β_2 -agonist more than once daily (6).

Corticosteroids produce their effect on responsive cells in asthmatic airways by activating glucocorticoid receptors (GR) to directly or indirectly regulate the transcription of certain target genes (1, 36). The GR are widely distributed within the human lung, with the greatest concentrations being located in the airway epithelial cells and bronchial vascular endothelial cells (1).

Corticosteroids decrease the number and activation status of a range of inflammatory cells, including airway eosinophils, T lymphocytes, macrophages, dendritic cells and mucosal mast cells (36,37).

The number of circulating eosinophils is effectively reduced by corticosteroid treatment and this may be due to a direct effect on eosinophil production in the bone marrow (1). Inhaled corticosteroids also inhibit the night-time increase in circulating eosinophils in patients with nocturnal asthma, with a concomitant reduction in nocturnal asthma symptoms. There is a marked reduction in the number of degranulated eosinophils after corticosteroid therapy, which is thought to result via inhibition of cytokine production in the airways (1,9).

The permissive action of cytokines such as GM-CSF and IL-5 on eosinophil survival is inhibited by corticosteroids and this contributes to a reduction in airway eosinophils (1). Corticosteroids are direct inhibitors of mediator release from eosinophils and weakly inhibit the release of reactive oxygen species and eosinophil basic proteins that cause bronchial damage (1). Additionally, corticosteroids block the release of cytokines from T lymphocytes, thus reducing the recruitment and survival of several inflammatory cells involved in airway inflammation (1).

The regular use of corticosteroids in steroid-dependent and non-steroid-dependent asthmatics is associated with a decrease in airway responsiveness. This improvement is reversible and the protective effect disappears after withdrawal of corticosteroid therapy, highlighting the need to continue this therapy (38).

Clinical experience with budesonide and formoterol

Clinical studies have shown that budesonide 100–800 µg twice daily administered by Turbuhaler® is effective and improves lung function in a dose–response fashion (39). However, in a previous study in patients with moderate asthma there was no clear dose–response for improvements in lung function with inhaled corticosteroids (40). Doubling of the dose of inhaled corticosteroids in uncontrolled asthma is a frequent solution to gaining control of asthma symptoms, but this rationale is not well supported in the literature.

The efficacy and safety of budesonide have been extensively covered in earlier reviews (41,42). More recently, budesonide has been shown to be effective in a number

of studies of patients with mild to moderate asthma (43–46). Budesonide therapy is also effective once or twice daily. In a number of studies, a single daily dose of budesonide was as effective as twice-daily dosing in improving lung function and asthma symptoms (44, 47–49). The therapeutic control of asthma symptoms achieved by budesonide over a range and frequency of doses makes it an ideal agent in the treatment of asthma, which varies in severity over time.

The efficacy of budesonide has also been demonstrated in children with asthma or recurrent wheezing (49–53). Short- and long-term studies have been carried out to evaluate the effect of budesonide on adrenal suppression and bone growth in children (54–56). Budesonide was well tolerated in these patients and there were no significant adrenal suppression or adverse effects related to bone growth (54–56).

The efficacy of formoterol has been demonstrated in both short- and long-term randomized, placebo-controlled trials. In one short-term study ($n = 43$; 2 weeks), formoterol 12 µg was more effective than formoterol 6 µg or placebo (57). In a second larger study ($n = 156$), formoterol 6, 12 and 24 µg significantly reduced asthma scores and the need for supplementary medication (58). Several long-term studies ranging from 12 to 25 months have also demonstrated the efficacy of formoterol 12 µg and 24 µg twice-daily (58–61). In all of these studies, patients treated with formoterol showed an improvement in lung function and improved asthma control without the need to increase the dose of formoterol or that of corticosteroids.

Inhaled formoterol is also efficacious in children with asthma; however, the majority of the early studies were of short duration (62). In one long-term study ($n = 82$; 1 year), clinical efficacy variables and lung function improved over the course of the study with no evidence of tachyphylaxis (59).

The efficacy of formoterol in addition to inhaled corticosteroid therapy has also been demonstrated in a long-term study ($n = 852$) in patients with poorly controlled asthma despite regular inhaled corticosteroid therapy (34). In this study formoterol plus budesonide treatment improved asthma symptoms and reduced the number of exacerbations more effectively than increasing the dose of budesonide alone. The improvements seen in the formoterol plus budesonide treated patients were achieved without lessening the control of asthma. Additionally, there is no evidence that the course of exacerbations of asthma is different during treatment with formoterol (63). Nor is there any evidence that formoterol masks inflammation, as low-dose budesonide plus formoterol and high-dose budesonide were equally effective in suppressing sputum eosinophils (64).

Other studies support the findings that the addition of a low-dose, long-acting β_2 -agonist to low- or moderate-dose corticosteroids is as effective or more effective

than high-dose corticosteroids, but without the long-term systemic effects associated with high corticosteroid doses (31,65–68).

THE FUTURE OF ASTHMATHERAPY

Given the complex mechanisms involved in the pathophysiology of asthma, it is not surprising that asthma treatment is associated with a range of different therapies, all of which need to be carefully tailored for the individual patient.

Indeed, new therapies have been added to asthma treatment as our understanding of the different aspects of the disease has increased. However, the use of multiple therapies necessitates a clear understanding of the mode of action of the drugs and any potential interaction or overlap of effect. For example, it is now clear that the long-acting β_2 -agonists and corticosteroids both have a controlling role in the treatment of asthma, but their cellular effects are complementary. Furthermore, there may be a positive interaction between these two classes of drugs, as corticosteroids may prevent tolerance to long-acting β_2 -agonists, and β_2 -agonists may increase the molecular effects of corticosteroids (69). The efficacy of formoterol administered as needed suggests that the concomitant use of a short-acting β_2 -agonist and formoterol has little clinical benefit. Acceptance of such an idea is an important step towards simplifying asthma management for both the doctor and patient.

The use of multiple drugs in the treatment of asthma can make asthma management complex. From the point of view of the patient, the more complicated their treatment the more difficult it is for them to adhere to their treatment plan. Without a clear understanding of their disease or while in a distressed state, a patient may even take the wrong medication by mistake. Thus treatment developments that pave the way to simplifying asthma treatment are a welcome addition to asthma therapy. One such development is the combination of an inhaled corticosteroid and long-acting β_2 -agonist in a single inhaler.

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